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Case Study

Aplastic Anemia induced by Nivolumab before a Treatment of Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia

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Abstract

As an Immune checkpoint blockade therapy (ICB), nivolumab has demonstrated efficacy in Acute Myeloid Leukemia (AML) and various other malignancies. Nivolumab is used as an anti-programmed cell death 1 (PD-1) agent. The toxicities are observed in more than 10% of patients, because of its ability, anti-PD-1 will upregulate the activity of T-cells. Over-activated T-cells will cause immune-related adverse events such as Aplastic Anemia (AA). Here, we present a case of an over 60-years old male patient with AML, and the possibility for him to receive an allogeneic hematopoietic stem cell transplantation (allo-HSCT). The patient was treated with nivolumab and subsequently developed AA. As an additional consideration, we will also discuss whether allo-HSCT is transplantable when AA is performed during the treatment of AML.

Keywords

Acute Myeloid Leukemia, Nivolumab, Aplastic Anemia, Allogeneic hematopoietic stem cell transplantation, Cytarabine, Idarubicin, Methylprednisolone.

Introduction

AML is a type of blood cancer with excess immature white blood cells in bone marrow. AML- associated regulatory T-cells (Tregs) will downregulate the function of adoptively transferred cytotoxic T-cells in vivo, and Tregs depletion followed by PD-1 inhibitor such as nivolumab will result in a superior anti-AML ability (Sehgal et al. 2015) This mechanism of nivolumab in AML is also likely to over-activate the T-cells which causes immune-related adverse events such as AA (Comito et al. 2017). Nivolumab is approved in the US for pre- and post- allo-HSCT treatment to prevent relapse and graft versus host disease (GVHD) (Herbaux et al. 2017). Immune-related adverse event AA presenting before allo-HSCT during the nivolumab treatment for AML could be an indication of relapse after HSCT. However, very limited research has been done to investigate how AA secondary to nivolumab therapy may affect the outcome of HSCT.

Case report

A 61-year-old Caucasian male was diagnosed with AML and detected mutations of DNA (cytosine-5)-methyltransferase 3 alpha (DNMT3A) by next-generation sequencing. The bone marrow biopsy was performed 3 months before presentation and found no evidence of AA; the patient had no personal or family history of AA. Laboratory investigations revealed white blood cell count (WBC) 44×109/L with 86% blasts, hemoglobin 8.1 g/dL and a platelet count of 37×109/L. After obtaining an informed consent, the patient was treated with an induction chemotherapy with IA regimen (cytarabine 1.5 g/m2 by vein daily on days 1-3, with idarubicin 12 mg/m2 by vein daily on days 1-3). After the first week of treatment, the patient's WBC count fell to 36×109/L with a significant decrease in blast cell count. The patient had diarrhea, dizziness and headache which was most likely caused by chemotherapy, according to the comprehensive review of systems. It reveals the patient reported no other adverse reaction besides common side effects of IA regimen from the chemotherapy.On day 8, the first dose of nivolumab (1 mg/kg by vein) was started without induction chemotherapy and continued every two weeks for 10 cycles. No adverse reactions developed nor was there any disease progression. On day 138, the 11th dose of nivolumab was administered, and patient's platelet count was 53×109/L. However, immediately after the 11th dose, there was a sudden decrease in platelet count to 32×109/L. As the following 12th dose of nivolumab was served, the patient's platelet counts gradually dropped to 5×109/L. This result may reveal bone marrow damage, and it was possibly attributed to the nivolumab treatment. The patient's bone marrow biopsy and aspirate was conducted. The images illustrated lacking of trilineage marrow elements, and

a hypocellular marrow with global trilineage hypoplasia, (Figs 1, 2) which are consistent with AA. From day 170 to day 179, the patient was administered with a high dose of methylprednisolone (2 mg/kg/day) intravenously, and from day 180 to 190, the dosage was reduced to 1 mg/kg/day. Patient responded well to the steroid therapy with recovered platelet and hemoglobin count. Due to the development of presumed grade 2/4 drug-mediated autoimmune complication, the patient responded well to the steroid therapy. In this case, stop administrate nivolumab during the AML treatment, will put patient at high risk for relapse. After all the consideration, the patient was restarted on nivolumab on day 216 and 229, the 13th and 14th dose of nivolumab was administered, WBC count increased to 52×109/L with less than 10% blast cell counts (Fig. 3). Although the minimal residual disease (MRD) monitoring has significance impact on prognostic, it remains to be determined which molecular markers are the most suitable for MRD monitoring, but unfortunately, for DNMT3A mutations were not correlated to relapse after long follow up clinical studies, DNMT3A is very unlikely suitable for any specific MRD detection (Ossenkoppele and Schuurhuis 2016). Additionally, DNMT3A mutation leads to abnormal of DNA methylation patterns, which is likely to alter the expression of the various target genes which indicate their applicability MRD monitoring remains unclear (Debarri et al. 2015). After all the consideration, whether allo-HSCT is transplantable should be discussed with more discretion. The profile of the patient is provided (Table 1).

Table 1.

The patient characteristics .

The patient characteristics in with AA induced by nivolumab therapy	
Gender/age	Male/61
Hematology-Oncology	Acute Myeloid Leukemia with DNMT3A mutation.
Baseline CBC *Hb (g/dL)* *Plt (×10^9/L)* *WBC (×10^9/L)*	 8.1 37 44
ICB agent/dose	Nivolumab (1mg/kg/two weeks)
Presentation of AA	151 days post 12th cycles of Nivolumab.
AA presentation *Hb (g/dL)* *Plt (×10^9/L)* *WBC (×10^9/L)*	 6.1 5 12
BM biopsy	The biopsy of BM reveals the bio-sample lack of hematopoietic elements and hypocellular marrow.
Treatment of AA	Methylprednisolone ×21 days.
AA response	Rapid recovery in hemoglobin and neutropenia on day 177.
Patient outcome	The patient has reached complete remission, no other adverse reaction is developing and further HSCT should be considered.

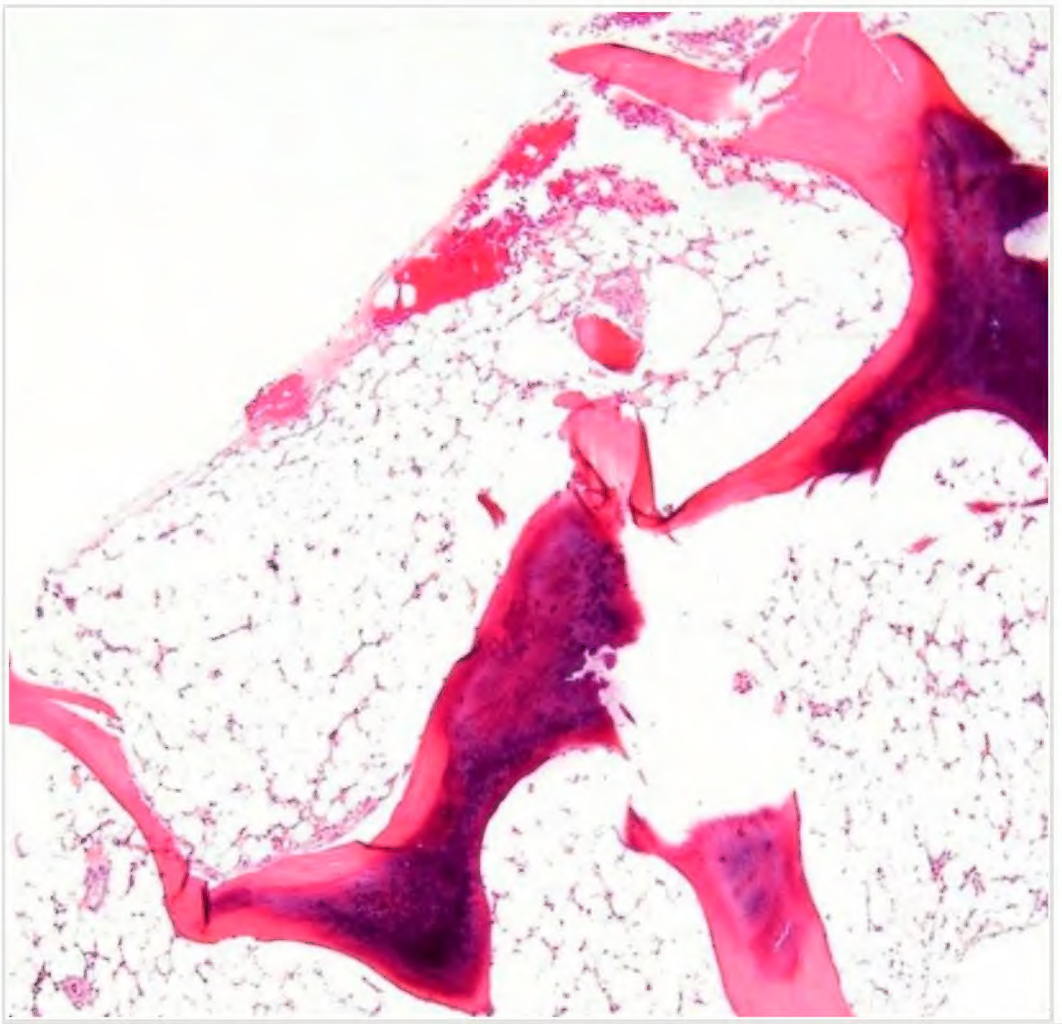

Figure 1.

Demonstrated a hypocellular marrow with global trilineage hypoplasia.

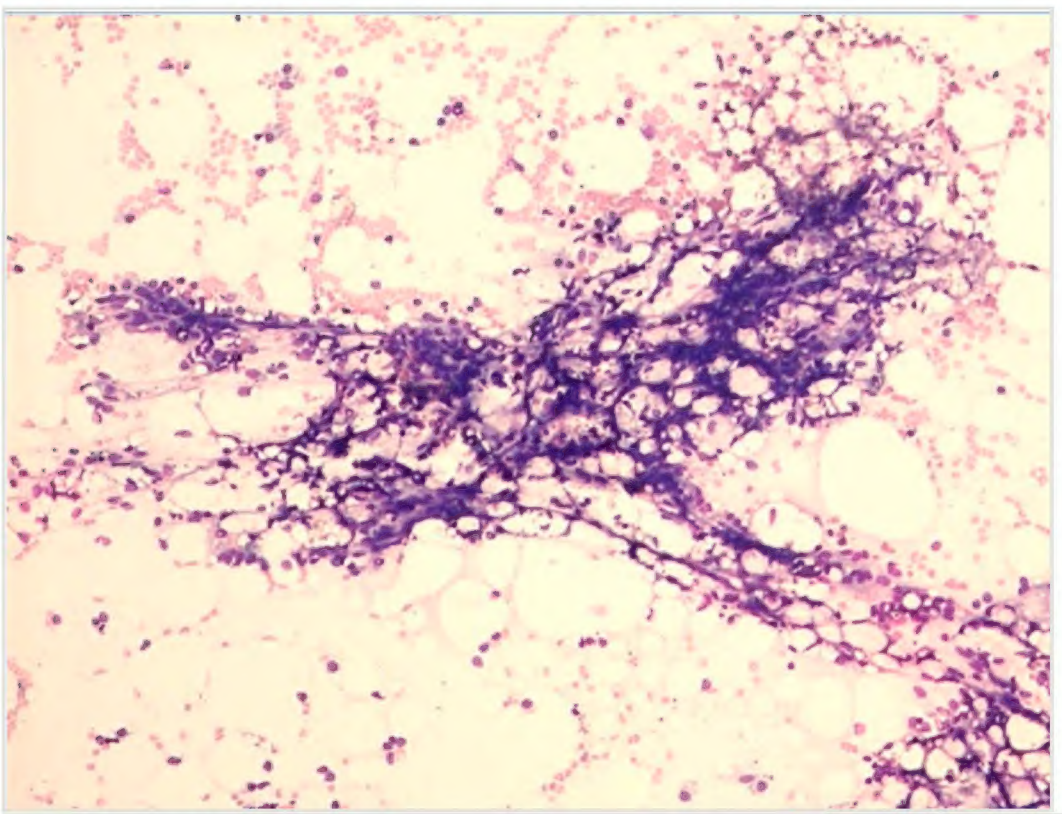

Figure 2.

BM aspirate demonstrated a spicules composed of stromal components, but lacking trilineage marrow elements.

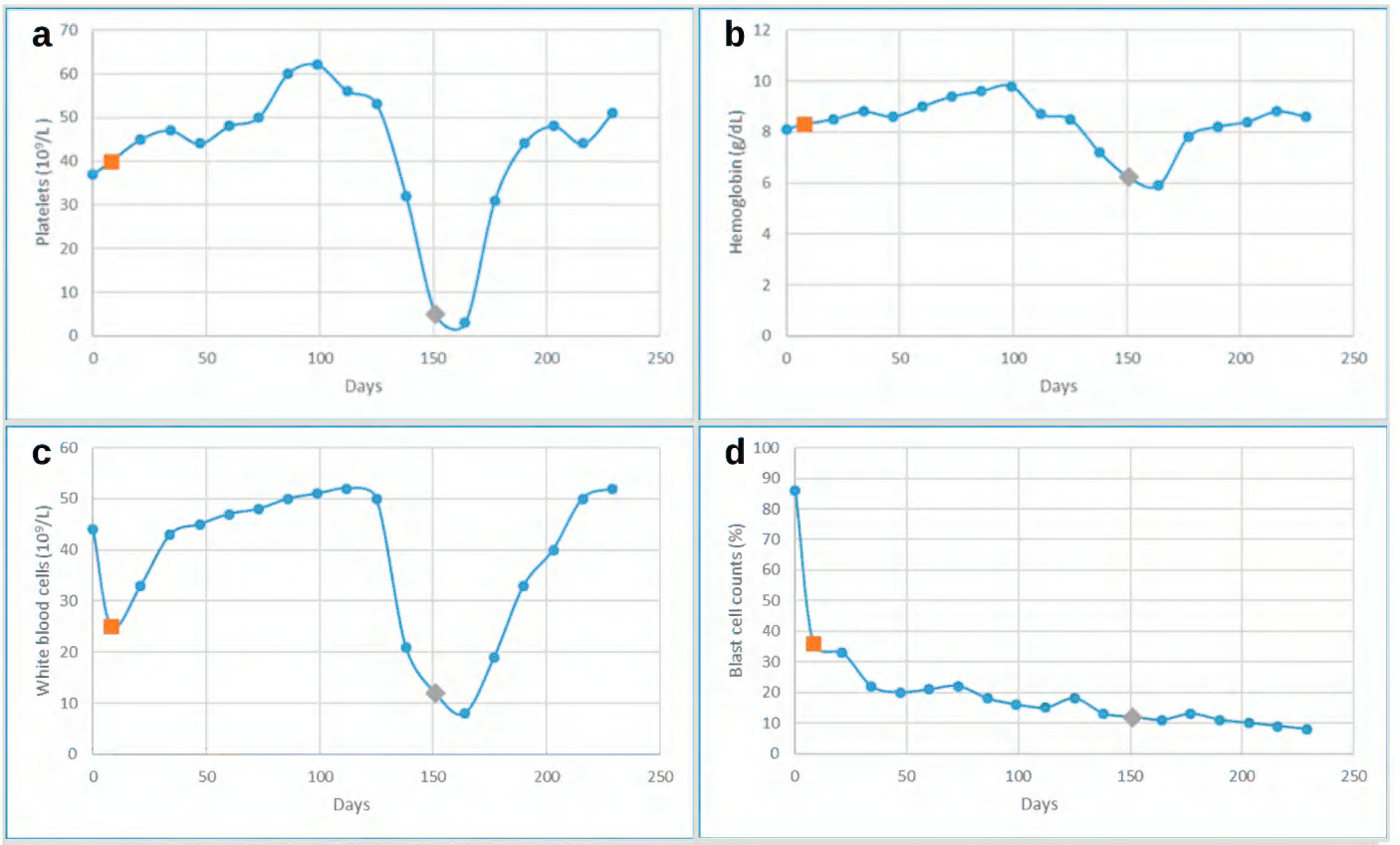

Figure 3.

Efficacy of chemotherapy, nivolumab and methylprednisolone in patient.

After one week DA regimen chemotherapy, patient was stared nivolumab therapy without continuing chemotherapy. After the 12th dose of nivolumab was administered an AA was detected. These graph provide last 229 days clinical dates of patient's platelet, hemoglobin, WBC and blast cell count.

Organge Box: 1st nivolumab was administered.

Grey diamond: Aplastic anemia was detected.

a: Patient's platelet count variation graph
b: Patient's Hemoglobin variation graph
c: Patient`s White blood cell count variation graph
d: Patient`s Blast cell count variation graph

Discussion

Addition of nivolumab to IA regimen is safe in older AML patients; although, it may cause immune-related adverse events such as AA. Patients with AA receive a destruction of hematopoietic cells by over-activated immune system leads to pancytopenia. Somatic mutations, DNMT3A-mutated genes, were detected in some of the AML or AA patients (Kulasekararaj et al. 2014), but clinical work-up and later laboratory investigation illustrated the patent did not develop AA before the treatment, and it happened after the 11th dose of nivolumab was received. After AA was developed, it may have revealed PD-1 inhibitor; nivolumab is over-activating T-cells, and consequently causes bone marrow damage. Even though at this case, immune-mediated bone marrow destruction is reversible by immunosuppression or withdrawal of the offending agent, but using immunosuppressive drugs such as methylprednisolone may lead to delayed immune reconstitution after

process allo-HSCT to increase the risk of relapse (Perales and van den Brink 2012). In this case report, methylprednisolone was administered as an immunosuppression treatment, and it could downregulates activates of T-cells. If the patient has been processed allo-HSCT, the recovery of T cell compartment relies on the peripheral expansion of memory T-cell (T lymphocyte), eventually leads to a slow T-cell reconstitution and consequently causing the relapse (Krenger et al. 2011). However, nivolumab has been approved in the US to prevent relapse after allo-HSCT. Continuing to administer nivolumab at post stage of allo-HSCT may specifically help slow T-cell reconstitution-related immune complications or relapse (Ogonek et al. 2016). Due to the limited amount of research and knowledge on this clinical case, more studies are needed for further actions on allo-HSCT.

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Ethics and security

This clinical research and patient recruitment is following the ethics and regulations, which includes: Nuremberg Code (1947), Declaration of Helsinki (2000), Belmont Report (1979), CIOMS (2002), U.S. Common Rule (1991).

Reviewed by Institutional Review Board

NAME: Geisinger Institutional Review Board

IRB REGISTRATION #: 00008345

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FWA ASSURANCE: FWA00000063

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Conflicts of interest

The patients and author declares that they have no potential conflicts of interest.

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